REMARKS

Claims 22-24, 27-32, 37, 39-40 and 60 are pending. Claims 22, 27 and 60 are amended herein. Claims 1-21, 25-26, 33-36, 38, 41-59 and 61-95 are cancelled. Applicants reserve the right to file divisional/continuation applications to the cancelled subject matter. Basis for the amendments can be found in the application and claims as originally filed. For example, basis for the amendment to claims 1, 27 and 60 can be found on page 5, lines 10-13. No new matter is added.

Provided herewith is a supplemental information disclosure statement and PTO Form 1449.

Also provided is a Declaration of Dr. Alan Snow. The Declaration provides data in APP Transgenic mice that demonstrates that the *in vitro* data provided in the application correlates to and is predictive of the *in vivo* data. The data provided in the Declaration demonstrates prevention of brain amyloid formation/accumulation by procyanidin B, reduction in amyloid load/plaque number in APP Transgenic Mice after treatment with procyanidin B2, reduction in amyloid load/plaque number after treatment with procyanidin B2, reduction/inhibition of brain Aß 42/40 levels by procyanidin B2, reduction in microgliosis in APP Transgenic Mice after treatment with procyanidin B2 and improvement in hippocampus-dependent memory (spatial acquisition) as determined by Morris Water Maze Testing. Therefore, the *in vitro* data provided in the application correlates to and is predictive of the *in vivo* activity of procyanidin B2.

THE REJECTION OF CLAIMS 22-36, 38-49, 52, 53 and 57-61 UNDER 35 U.S.C. §102(b), OVER CASTILLO *ET AL.*

Claims 22-36, 38-49, 52, 53 and 57-61 are rejected under 35 U.S.C. § 102(b) as being anticipated by Castillo *et al.* (International Patent Application Publication No. WO/0012102) because the cited reference allegedly discloses using procyanidin B2 in the treatment of Alzheimer's disease.

Applicants note that claims 1-21, 25-26, 33-36, 38, 41-59 and 61-95 are cancelled herein. The rejection is respectfully traversed with respect to pending claims 22-24, 27-32, 37, 39-40 and 60.

Disclosure of International Patent Application Publication No. WO/0012102 by Castillo *et al.*

Castillo *et al.* discloses the use of a product obtained from the inner bark and/or roots from the plant Uncaria Tomentosa in combination with one or more other ingredient listed therein in the compositions and methods for treating Alzheimer's disease amyloidosis and for improved brain cognition, memory/ recall optimization. The reference does not disclose use of procyanidin B2 in the compositions and methods disclosed therein.

Differences between the disclosure of the cited reference and the instant claims

Claims 22-24

As amended herein independent claim 22 is directed to a method for treating the formation, deposition, accumulation, or persistence of amyloid fibrils in a mammal, by treating the fibrils with an effective amount of a procyanidin B2 wherein the effective amount is between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight of the mammal per day. Claims 23 and 24 depend from claim 22 and further define the method of claim 22.

As discussed above, the cited reference discloses compositions containing the products obtained from the inner bark and/or roots from Uncaria tomentosa and additional blended ingredients. The reference further describes methods of using those compositions for treatment of amyloid formation, deposition, accumulation and/or persistence in Alzheimer's disease, type II diabetes and other amyloidoses. The reference does not disclose using procyanidin B2 in the methods described therein. Furhter, the reference does not disclose treating the formation, deposition, accumulation, or persistence of amyloid fibrils in a mammal with procyanidin B2 in an amount ranging from between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight of the mammal per day as instantly claimed. Since the reference does not disclose all elements of the claimed method, the reference does not anticipate claim 22 or any of the dependent claims.

Claims 27-32 and 37-40

Independent claim 27 is directed to a method for treating an amyloid disease in a mammal by administering a therapeutically effective amount of a procyanidin B2 to the mammal wherein the effective amount is between about 0.1 mg/kg of body weight per day and about 1000

mg/kg of body weight per day. Claims 28-32 and 37-40 depend from claim 27 and further define the method of claim 27.

The cited reference does not disclose using procyanidin B2 in a method for treating an amyloid disease in a mammal. The reference further does not disclose treating amyloid disease in a mammal with procyanidin B2 in an amount ranging from between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight of the mammal per day as instantly claimed. Since the reference does not disclose all elements of the claimed method, the reference does not anticipate claim 27 or any of the dependent claims.

Claim 60

Independent claim 60 is directed to a pharmaceutical composition containing procyanidin B2 and a pharmaceutically acceptable excipient, wherein the amount of procyanidin B2 in the composition is sufficient to deliver between about 1 mg/kg of body weight per day and about 1000 mg/kg of body weight per day to a mammal in a single dose

The cited reference does not disclose compositions containing procyanidin B2. Nor does the reference disclose compositions containing procyanidin B2 in an amount sufficient to deliver between about 1 mg/kg of body weight per day and about 1000 mg/kg of body weight per day to a mammal in a single dose. Since the reference does not disclose all elements of the claimed composition, it does not anticipate claim 60.

CLAIM REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH: LACK OF WRITTEN DESCRIPTION

Claims 22-49, 52, 53 and 57-61 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement. The Office Action alleges that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Office Action then provides analysis of Wands factors to support the rejection. Applicants respectfully request reconsideration of the rejection in view of the amendments and arguments herein.

Analysis

First, applicants note that the Office Action is mixing the criteria to satisfy the written description and enablement requirements. The Office Action alleges that the claims are rejected

for lack of written description and provides analysis of Wands factors to support the rejection. Applicants submit that the Wands factors are irrelevant to satisfy the written description requirement. As discussed below, the instant claims satisfy the written description requirement. Furthermore, as discussed below, the instant claims are enabled by the disclosure in the application.

Written Description

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the claimed subject matter. To satisfy the written description requirement, a patent specification must describe the claimed subject matter in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed subject matter. See, *e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

Claims 22-24

Instant claims 22-24 are directed to methods for treating the formation, deposition, accumulation, or persistence of amyloid fibrils in a mammal, by treating the fibrils with an effective amount of a procyanidin B2 wherein the effective amount is between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight of the mammal per day. The claimed methods are fully described throughout the specification and claims as originally filed. For instance, such methods are described in the specification at, for example, page 5, lines 16-18, page 6, lines 14-17 and page 34, lines 21-23. Further, the specification describes various assays in Examples 7-9, 14 and 15 to measure the desired activity in the claimed methods.

Since instant claims 22-24 are fully described by the specification and claims as originally filed, Applicants respectfully request that the rejection of claims 22-24 under 35 U.S.C. § 112, first paragraph, for lack of written description, be withdrawn.

Claims 27-32 and 39-40

Instant claims 27-32 and 39-40 are directed to methods for treating an amyloid disease in a mammal by administering a therapeutically effective amount of a procyanidin B2 to the mammal wherein the effective amount is between about 0.1 mg/kg of body weight per day and about 1000 mg/kg of body weight per day. The claimed methods are fully described throughout the specification and claims as originally filed. For instance, such methods are described in the

specification at, for example, see application page 4, line 19 through page 5, line 13 and original claims. Since instant claims 27-32 and 39-40 are fully described by the specification and claims as originally filed, Applicants respectfully request that the rejection of claims 27-32 and 39-40 under 35 U.S.C. § 112, first paragraph, for lack of written description be withdrawn.

Claim 60

As discussed above, instant claim 60 is directed to a pharmaceutical composition containing procyanidin B2 and a pharmaceutically acceptable excipient, wherein the amount of procyanidin B2 in the composition is sufficient to deliver 1 mg/kg of body weight per day and about 1000 mg/kg of body weight per day to a mammal. The specification describes such compositions on pages 34-37. Since instant claim 60 is fully described by the specification as originally filed, Applicants respectfully request that the rejection of claim 60 under 35 U.S.C. § 112, first paragraph, for lack of written description, be withdrawn.

Enablement

The Office Action alleges that in view of the Wands factor and *In re* Fisher, one of ordinary skill in the art would have to engage in undue experimentation to test which disease can be treated by the compounds of the instant claims with no assurance of success. Applicants respectfully traverse the allegation.

The test for enablement is whether or not any person skilled in the art could make and use the claimed subject matter from the disclosure in an application, coupled with information known in the art, without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). Applicants submit that the present specification teaches how to make procyanidin B2 used in the claimed methods (for example, see, Examples 1-6), teaches pharmaceutical compositions containing procyanidin B2 and teaches how to administer the compound and compositions (see pages 34-37). Further, Applicant has addressed the Examiner's specific concerns below.

1. The nature of the invention

The instant claims are directed to methods for treating the formation, deposition, accumulation, or persistence of amyloid fibrils and methods for treating amyloid disease using procyanidin B2 and compositions containing procyanidin B2 in the amounts recited therein.

2. The breadth of claims

The Office Action alleges that the claims are directed to the treatment of any and all diseases mediated by the amyloid fibrils and synuclein fibrils.

Applicants note that the claims as amended herein, do not recite synuclein fibrils. The claims are directed to the treatment of the formation, deposition, accumulation, or persistence of amyloid fibrils and treatment of amyloid disease by administering procyanidin B2 in the amounts specified in the claims. The application defines, on page 13, lines 4-11, treatment of a disease includes preventing the disease from occurring in a mammal that may be predisposed to the disease but does not yet experience or exhibit symptoms of the disease (prophylactic treatment), inhibiting the disease (slowing or arresting its development), providing relief from the symptoms or side-effects of the disease (including palliative treatment), and relieving the disease (causing regression of the disease). It is further described that "treating" amyloidosis or amyloid diseases includes any one or more of the following: preventing, inhibiting, reducing, disassembling, disrupting, and disaggregating amyloid fibrils and amyloid protein deposits, such as Aβ and the other amyloids. Therefore, the claims are limited to specific uses of a specific compound and are not broad as suggested in the Office Action. Nevertheless, the Federal Circuit has stated that with respect to the breadth of claim as it pertains to enablement, the only relevant concern should be whether the scope of enablement provided by the disclosure is commensurate with the scope of the claims. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003). Applicants submit that the enablement of the present disclosure is commensurate with the scope of the pending claims as the disclosure teaches how to prepare the compounds used in the claimed methods and how to use the compounds in the methods.

3. The state of the prior art and the predictability in the art

The Office Action alleges that the state of the prior art is such that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. It is further alleged that the unpredictable nature of pharmacological art requires each embodiment to be individually assessed for physiological activity. The Office Action urges that in the absence of showing of a nexus between amyloid fibrils, synuclein fibrils and useful treatment of Alzheimer's disease, one of ordinary skill in the art is unable to fully predict possible results from the administration of the compound in the methods claim 1.

First, applicants submit that the instant claims are directed to methods of treatment using **a specific compound, procyanidin B2**. Therefore, screening of compounds to determine which compound exhibits the desired pharmacological activity is not needed and is irrelevant.

Second, it is well known in the art that amyloid refers to a group of diverse but specific extracellular protein deposits which all have common morphological properties, staining characteristics, and X-ray diffraction spectra. As described in the application and known in the art, for example, *see* the attached article by Soto in *FEBS Letters*, **498**, 204-207 (2001), the amyloids include, but are not limited to, the amyloid associated with Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis of the Dutch type and inclusion body myositosis (where the specific amyloid is referred to as beta-amyloid protein or Aβ), the amyloid associated with chronic inflammation, various forms of malignancy and familial Mediterranean fever (where the specific amyloid is referred to as AA amyloid or inflammation-associated amyloid), the amyloid associated with multiple myeloma and other B-cell dyscrasias (where the specific amyloid is referred to as AL amyloid), the amyloid associated with type 2 diabetes (where the specific amyloid is referred to as amylin or islet amyloid), the amyloid associated with the prion diseases including Creutzfeldt-Jakob disease, Gerstmann-Straussler syndrome, kuru, and scrapie (where the specific amyloid is referred to as PrP amyloid), the amyloid associated with long-term hemodialysis and carpal tunnel syndrome (where the specific amyloid is referred to as β2-microglobulin amyloid), the amyloid associated with senile cardiac amyloid and familial amyloidotic polyneuropathy (where the specific amyloid is referred to as prealbumin or transthyretin amyloid), and the amyloid associated with endocrine tumors such as medullary carcinoma of the thyroid (where the specific amyloid is referred to as variants of procalcitonin).

Applicants respectfully submit that the conditions associated with amyloid diseases and recited in the claims have shared characteristics and at least one common etiology because each is associated with extracellular amyloid deposition. The amyloid deposition is implicated in numerous and diverse disease settings. Enclosed herewith are copies of peer-reviewed literature publications which indicate that amyloid deposition is responsible for a variety of diseases. Prevention/ inhibition of amyloid deposition may provide clinical benefit in such diseases. For example, the article by Porat *et al.* (submitted herewith) indicates that inhibitors of amyloid fibril

formation may be useful as therapeutic agents in treatment of amyloid diseases. Thus, amyloid deposition is known to be associated with numerous diseases, including Alzheimer's and other diseases and the compounds that prevent or inhibit the formation, deposition, accumulation, or persistence of amyloid fibrils may provide clinical benefit in the disease associated with amyloidosis. Also, attached article by Ono *et al.*, describes that fibril-destabilizing activity of polyphenols provides basis for development of therapeutics for Alzheimer's disease and other human amyloidosis.

Applicants respectfully point out that the Federal Circuit has specifically stated that it is the Food and Drug Administration and not the PTO that determines the safety and efficacy of drugs for use in humans. *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995) (Testing for the full safety and effectiveness ... is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings). This regulatory process is not the same as the enablement requirement under 35 U.S.C. § 112. As demonstrated by the *in vitro* data in the application and the *in vivo* data provided in the Declaration of Dr. Alan Snow, procyanidin B2 treats formation, deposition, accumulation, or persistence of amyloid fibrils and is useful in treating amyloid disease.

4. The level of skill in the art is high

The level of skill in this art is recognized to be high (see, e.g., Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). In addition, the numerous articles and patents that are of record in this application that are authored by those of a high level of skill for an audience of a high level of skill further evidences the high level of skill in this art.

5. The amount of direction present

The Office Action alleges that the guidance present in the application is that of the compounds that are tested that some work and some don't work. It is alleged that very similar compounds have been shown to have one work and the other have no effect. Applicants disagree.

Applicants direct Examiner's attention to the fact the claimed subject matter is directed to use of **a specific compound**, procyanin B2, in the methods and compositions of the instant claims. The application does not provide any comparative data for procyanidin B2 with respect

to any other compounds and such comparison is irrelevant to the instant claims. Applicants respectfully submit that the application provides guidance on how to make and administer procyanidin B2 used in the instantly claimed methods. For example, isolation of procyanidin B2 from plant *Uncaria Tomantosa* and synthesis of procyanidin B2 is described in detain in Examples 1-6. The *in vitro* activity of procyanidin B2 in inhibition/disruption of Aβ amyloid fibrils is described in Examples 7, 8, 13 and 14. Based on this disclosure, one of skill in the art can use procyanidin B2 in the methods for treating the formation, deposition, accumulation, or persistence of amyloid fibrils, methods for treating amyloid disease and in the pharmaceutically compositions as instantly claimed. Therefore, the application provides ample guidance on how to make and use the full scope of the claimed subject matter.

Declaration of Dr. Alan Snow

Further, the Declaration of Dr. Alan Snow, submitted herewith, provides data in APP Transgenic mice that demonstrates prevention of brain amyloid formation/accumulation by procyanidin B, reduction in amyloid load/plaque number in APP Transgenic Mice after treatment with procyanidin B2, reduction in amyloid load/plaque number after treatment with procyanidin B2, reduction/inhibition of brain Aß 42/40 levels by procyanidin B2, reduction in microgliosis in APP Transgenic Mice after treatment with procyanidin B2 and improvement in hippocampus-dependent memory (spatial acquisition) as determined by Morris Water Maze Testing. Therefore, the *in vitro* data provided in the application correlates to and is predictive of the *in vivo* activity of procyanidin B2.

Conclusion

As discussed above, the instant specification describes the use procyanidin B2 in the methods for treating the formation, deposition, accumulation, or persistence of amyloid fibrils, methods for treating amyloid disease and in the pharmaceutically compositions as instantly claimed. The working examples in the specification demonstrate the *in vitro* activity of procyanidin B2 in inhibition/disruption of Aβ amyloid fibrils. The *in vivo* data in the attached Declaration of Dr. Alan Snow demonstrates prevention of brain amyloid formation/accumulation by procyanidin B in APP Transgenic Mice, reduction in amyloid load/plaque number in APP Transgenic Mice after treatment with procyanidin B2, reduction in amyloid load/plaque number after treatment with procyanidin B2, reduction/inhibition of brain Aß 42/40 levels by

procyanidin B2, reduction in microgliosis in APP Transgenic Mice after treatment with procyanidin B2 and improvement in hippocampus-dependent memory (spatial acquisition) as determined by Morris Water Maze Testing. Therefore, in light of the scope of the claims, the description and the working examples in the application, and the high level of skill of those in this art, it would not require undue experimentation to practice the full scope of the claims. Applicant respectfully requests reconsideration and removal of the rejection.

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In view of the above, allowance of the application is respectfully requested.

Applicant hereby petitions under 37 C.F.R. §1.136 for three (3) months extension of time. Please apply the Petition for Extension of Time Fee for three months of $510, Filing Fee of $180 for filing a Supplemental Information Disclosure Statement under 37 CFR 1.97 (c), any other charges or any credits to Jones Day Deposit Account No. 50-3013. .

Respectfully submitted,

Date: 2/1/06

Dale L. Rieger
Reg. No. 43,045

Jones Day
12750 High Bluff Drive, Suite 300
San Diego, California 92130
858-314-1188 (direct)
858-314-1200 (main)
858-314-1150 (facsimile)
drieger@jonesday.com